UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,811	07/20/2005	Jeffrey Kerns	PU60030	8253

20462 7590 02/23/2006

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
BERNHARDT, EMILY B	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/542,811	KERNS ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/20/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 4,9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 4 is garbled as written. Should "or" on the 1st line really be "is" ?

2. Third species appears to be incomplete as written. Note there is no "oxo" group on the piperazine ring unless the "[3-oxo-" in front of piperidinyl really is part of the piperazine ring. Clarification is needed.

3. All of the optional routes appearing at the end of claim 10 are not clearly defining the invention since no reactants are set forth or particular products formed or reaction conditions set forth. See routes (i), (ii) and (iii) in part. For the latter, what reactions conditions makes solvates? None is seen in the specification as far as the examiner can determine.

Claims 9 and 10 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

1.) The species in claim 9 are not seen to be within the scope of claim 1. Note that in claim 1 when A=N and R3 is a heterocycle, the "N" atom is not recited as part of the ring yet species in 9 appear to include said "N" atom;

2.) Claims 9 and 10 recite solvates and/or salts which are not included in claim 1.

Claims 1-8 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Scope of solvates permitted in claims 9 and 10 are not enabled. Generally not all solvents can form solvates with all compounds. There is no process enabling such a scope in the specification . If applicants disagree they should point out where such is present.

2. Specification is not adequately enabled for scope of piperazines claimed which can have a variety of heterocycles at variables R2 and R3 and are also included as optional substituents for substituted alkyls,cycloalkyls in R1-R3. Said rings can carry up to 4 hetero atoms in any array and be further fused. Compounds made and presumed tested (although actual test data is not seen) correspond to R2 as cyclohexyl with R3 heterocycles formed with "A" as N being piperazine, morpholine and pyrrolidine.Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement

requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves binding to neurokinin (NK-2, NK-3 or both) receptors. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18. A range of IC50 values is reported which is enormous- covering from 1nM to 1000nM for NK-2 antagonistic activity .Such a 1000 fold range is not informative as to what structural modifications will yield lead compounds for further testing. Note Ohnmacht cited by the examiner discusses a lead compound having a IC50 value of 11nM. See section on "NK2 ANTAGONISTS" on p.75;

3) Direction or guidance- as stated above the compounds made are not representative of the instant scope but are closer to each other than to remaining scope ;

4) State of the prior art- The compounds are piperazine derivatives having carboxy- or carboxamidoalkyls on one end and substituted with quinolinylalkyl on the other N terminus. While such compounds are known as evident from the art applied below, they are similar in structure to the compounds made herein and thus do not evidence the many structural permutations permitted in the instant scope are known for at least one use in the prior art;

5) Working examples- Actual test data has not been presented and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There is no evidence that any piperazines instantly embraced have the ability to treat whole classes of respiratory diseases covered by the claim. The scope is vast including diseases pertaining to humans as well as other animals such as HIV- and FeLV-associated respiratory illness as well as lung diseases of unknown cause. No evidence is presented that instant compounds have

such a myriad of capabilities. The Ohnmacht publication provided with this action emphasizes how preliminary the findings are regarding various NK receptors. See pages 75-76 which discusses some limited applications for NK-2 antagonists, namely coughing, bronchoconstriction while for NK-3 antagonsists, it is stated that studies of such have been limited. Also note Pattachini who discussed positive results for bronchoconstriction . See concluding sentence in section 3.1 on p.16. With regard to Nk-3 antagonists, it is stated in the "Conclusions" section (on p.18) the following: "...but their role in human peripheral nervous system is much less documented".

Thus work in this area is only in the preliminary stages and such uses are not considered all treatable **much less preventable** based simply on NK-2 and/or NK-3 receptor binding antagonistic activity. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Note MPEP. 2164.05(a) .

Note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Level of unpredictability in the art- see discussion in the above par.one rejection for compounds;

2) Direction or guidance- The amount of guidance presented in the specification as to which compounds are sufficiently active to be useful for the claimed uses is nonexistent. The dosage range information (on p.29) is virtually useless being a 50 fold range and not directed to a specific disease;

3) Working examples- No test data has been presented for a specific disease state only assay testing which is not usually predictive of *in vivo* efficacy.

In view of the above considerations, this rejection is being applied.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farina (WO'165). The commonly assigned WO publication has a publication date which precedes applicants' earliest foreign priority date. It

describes the same type of compounds as NK antagonists. See formula (I) beginning on p.3 through p.5. While compounds such as the 5th and 6th species on p.12 do not anticipate the instant scope, they are obvious variants since oxo is also taught can be present on piperazine ring. Claim 4 requires that R3 be methyl which is also taught by Farina. See definition of R10 on p.4. Also, Farina teaches the same type of substitution on phenyl at instant R4 and also the same process of making is described on p.21-22. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify at various locations as described above the closest exemplified compounds in Farina and in so doing arrive at many more additional compounds that would be expected to be active as NK-2 and/or NK-3 antagonists in view of the equivalency teachings outlined above and their preparation by way of claimed process an obvious expedient.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 and 10-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/432925. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is overlapping subject matter between the two sets of claims as the copending case is the US equivalent of WO Farina applied above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/432925, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this

issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

E Bernhardt

Emily Bernhardt
Primary Examiner
Art Unit 1624